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Research Article

DRUG INDUCED STEVENS JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS: A STUDY BY SPONTANEOUS ADVERSE DRUG REACTION REPORTING SYSTEM

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A B S T R A C T

Stevens Johnson Syndrome (SJS) and Toxic epidermal necrolysis (TEN) are severe adverse cutaneous drug reactions that predominantly involve the skin and mucous membranes. Drugs are most commonly implicated and present study focuses on spontaneous adverse drug reaction reporting of drug induced SJS and TEN by using suspected adverse drug reaction reporting form provided by Pharmacoviglance Program of India (PvPI). Total of 18 adverse drug reactions of SJS, TEN and SJS-TEN overlap reports were collected from Rajiv Gandhi Government General Hospital & Madras Medical College, Chennai from May 2015 to October 2018. Among 18 ADR reports collected, 11 were SJS, 3 were TEN and 4 were SJS-TEN overlap cases. Out of 18 reports, 8 were female patients and 10 were male patients in the age group of 3-19 yrs (F-6, M-1) and 20-60 yrs (F-2, M-9). Total of 22 drugs were the offending drugs and 4 reports were found with multiple drugs and 14 were implicated with single drug. It was found that the most implicated class of drugs were antiepileptic drugs (n=8) followed by NSAIDs (n=4) and antimicrobials (n=2) as single offending drugs. All the reports fall under "probable" category according to WHO-UMC causality assessment scale, all were serious cases and all the patients recovered.

INTRODUCTION

Adverse drug reactions (ADRs) are important in healthcare as they account for 6% of hospital admissions, increase in economic burden on healthcare system, withdrawal of the drug from the market and death. Among the various ADRs, cutaneous adverse reactions like skin rashes, urticaria, itching, fixed drug eruptions, angioedema, erythema multiforme, *Stevens Johnson Syndrome* (SJS) and *Toxic Epidermal Necrolysis* (TEN) are the common ones (Barvaliya *et al*., 2011).

Stevens-Johnson syndrome (SJS) was first described in 1922 by the pediatricians *A. M. Stevens* and *F. C. Johnson*, as an acute mucocutaneous syndrome in two young boys. The condition was characterized by fever, inflammation of the buccal mucosa, severe purulent conjunctivitis, severe stomatitis with extensive mucosal necrosis, and purpuric macules. It became known as SJS and was recognized as a severe mucocutaneous disease with a prolonged course and potentially lethal outcome that is in most cases drug-induced (Harr and French, 2010, Ramya sree *et al*., 2017).

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Later in 1956, Alan Lyell described four patients with an eruption resembling scalding of the skin which he called toxic epidermal necrolysis or TEN. It was only as more patients with TEN were reported in the years following Lyell's original publication, that it became clear that TEN was drug induced, and that certain drugs such as sulfonamides, pyrazolones, barbiturates, and antiepileptics were the most frequent triggers of TEN (Harr and French, 2010).

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare immune-complex-mediated type-IV hypersensitivity reaction, but potentially life-threatening reactions to medications. Both conditions have significant morbidity and mortality and are considered to be clinical entities within a spectrum of adverse cutaneous drug reactions of increasing severity based on their surface of skin detachment. SJS and TEN are similar clinically and pathologically but differ only by severity of diseases (Tan & Tay, 2012, Ramya sree *et al*., 2017).

Medications that have traditionally been known to lead to SJS and toxic epidermal necrolysis include barbiturates (phenobarbital), anticonvulsants (carbamazepine, phenytoin, lamotrigine), allopurinol, sulphonamides, penicillins, cephalosporins, quinolones, NSAIDs (Chandaluri *et al*., 2018, Saganuwan, 2017).

Non-steroidal anti-inflammatory drugs (NSAIDs) are a rare cause of SJS in adults; the risk is higher for older patients, women and those initiating treatment. Typically, the symptoms of drug-induced SJS arise within a week of starting the medication. People with systemic lupus erythematosus or HIV infections are more susceptible to drug-induced SJS.[5] Genetic susceptibility is observed in Han Chinese as exemplified by the human leukocyte antigen HLA-B 1502, and SJS induced by carbamazepine (Saganuwan, 2017).

Aim & Objectives

To assess and present the drug induced Stevens Johnson Syndrome and Toxic Epidermal Necrolysis by spontaneous ADR reporting system

METHODOLOGY

A prospective non-interventional observational study was conducted from May 2015 to October 2018 at Madras Medical College and Rajiv Gandhi Govt. General Hospital, Chennai by using Suspected Adverse Drug Reaction Reporting form provided by Pharmacovigilance Program of India (PvPI). The clinicians and support staff was oriented towards the importance of pharmacovigilance and spontaneous reporting system by conducting lectures and meetings.

All the spontaneous ADR reporting forms pertaining to drug induced SJS and TEN were analyzed for the patient age group, gender, seriousness of the ADR, drugs implicating SJS & TEN and the causality assessment (WHO-UMC scale).

RESULTS

Total of 18 adverse drug reactions of SJS, TEN and SJS-TEN overlap reports were collected by spontaneous reporting system during the period of May 2015 to October 2018. Among 18 ADR reports collected, 11 were SJS, 3 were TEN and 4 were SJS-TEN overlap cases (Fig 1).

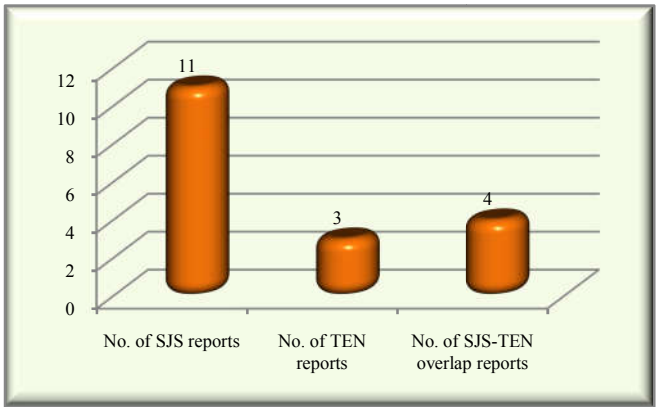

Fig 1 Number of SJS, TEN & SJS-TEN overlap reports

Out of 18, 8 were female patients and 10 were male patients in the age group of 3-19 yrs (F-6, M-1) and 20-60 yrs (F-2, M-9) (Fig 2).

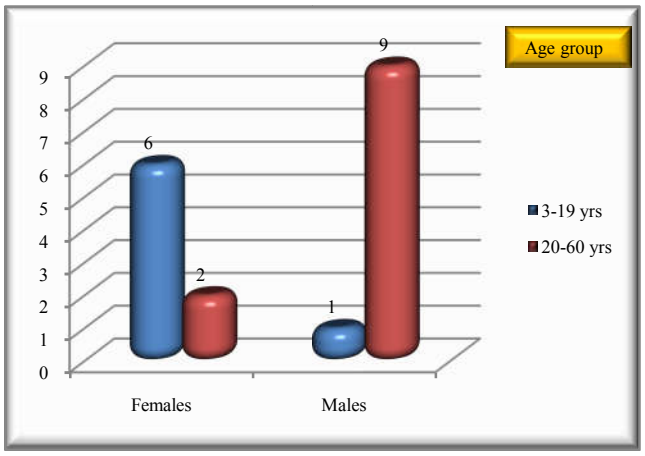

Fig 2 Age group of patients with SJS, TEN & SJS-TEN overlap

Total of 22 drugs were the offending drugs and 4 reports were found with multiple drugs and 14 were implicated with single drug (Table 1). It was found that the most implicated class of drugs were antiepileptic drugs (n=8) followed by NSAIDs (n=4) and antimicrobials (n=2) as single offending drugs. All the reports fall under "probable" category according to WHO-UMC causality assessment scale, all were serious cases and the all patients had recovered.

Table 1 Drugs that implicated SJS, TEN & SJS-TEN overlap

Name of the drug(s)	No. of reports
Phenytoin	SJS-5, SJS-TEN overlap-1
Carbamazipine	SJS-2
Diclofenac	SJS-1, SJS-TEN overlap -1
Nimesulide	TEN-1
Aceclofenac	SJS-1
Ciprofloxacin	SJS-1, TEN-1
Sulfasalazine, Celicoxib	SJS-TEN overlap -1
MOXCV, MEFMIN	SJS-1
Nimodipine, Phenytoin	TEN-1
Paracetamol, Amoxicillin	SJS-TEN overlap -1

DISCUSSION

In this study, the predominance was found to be more in males (n=10) than the females (n=8) and similar findings were shown in earlier studies *Tripathi C at al, Devender at al* and *Naveen K N et al* but is in contrast to other studies *S K Tan et al* and *Tejas K et al* . The most implicated class of drugs causing SJS, TEN and SJS-TEN overlap were found to be antiepileptic drugs (n=8) followed by NSAIDs (n=4) and antimicrobials (2) in the present study but it is in contrast to *Tejas K et al and Gomathy S et al* but was similar to the findings of *Rahima S et al* . Among the antiepileptic drugs, Phenytoin (n=6) is the most commonly implicated drug followed by Carbamazepine (n=2) which is contrary to the findings of *S K Tan et al*[3], *Rahima et al* and *Naveen K N et al*.

CONCLUSION

Concluding the present study that the SJS,TEN and SJS-TEN overlap are serious adverse drug reactions mostly implicated by antiepileptics, NSAIDs and early withdrawal of the offending agent and definitive treatment of SJS/TEN may reduce the morbidity, mortality rates and thereby, duration of hospital stay. Since the number of cases studied is less, it warrants further research.

Limitatins

There are several limitations to this study. As this non-interventional observational study was based on the spontaneous ADR reporting system only, there was an absence of a control group and lack of denominator data, i.e., total number of prescriptions with suspected drugs in study population. So, we could not quantify the risk of SJS/TEN associated with the use of medication. There is also the strong possibility of under-reporting.

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